# Zinc Metabolism and Its Implications in Clinical Medicine

PHILIP A. WALRAVENS, MD
*Denver*

DISTURBANCES IN ZINC HOMEOSTASIS are being reported in increasing numbers. Concomitantly "nutritional support" with zinc and other vitamin and mineral supplements is currently being advertised as adjunctive treatment in conditions where dietary intake has been inadequate. Some examples include conditions such as alcoholism, major burns, prolonged infections, massive trauma and repeated surgical interventions. Furthermore, within the past five years, two separate disorders of zinc metabolism have been recognized[1,2] and the standard American diet has been calculated to be on occasions marginal or deficient in zinc.[3]

Studies in humans presently indicate that zinc is needed for achievement of normal growth, for normal sexual maturation and function, and for maintenance of a normal appetite and taste acuity. Wound-healing, normal psychocognitive function and preservation of the integrity of epithelial surfaces also depend on an adequate nutritional intake of zinc.

Zinc is a trace element—that is, an element that forms less than 0.01 percent of the body weight—whose essentiality as a nutrient for mammals was discovered more than 40 years ago. Because this metal is fairly ubiquitous, human deficiencies of nutritional origin were considered improbable. In 1961, however, Prasad suggested that a syndrome of dwarfism and hypogonadism, seen in adolescents in Iran, might be caused by a nutritional deficiency of zinc,[4] and attention was drawn to the possibility of zinc deficiency in man.

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From the Department of Pediatrics, University of Colorado Medical Center, Denver.

Reprint requests to: Philip A. Walravens, MD, Department of Pediatrics, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver, CO 80262.

In this article, pertinent aspects of zinc metabolism and biochemical functions in humans will be reviewed, with reference, when necessary, to animal studies. The disease states in which zinc supplementation may be useful will then be discussed.

## Body Content and Distribution

The total body content of zinc in a hypothetical 70-kg (154-pound) man approximates 2.5 grams, with 30 percent of the total zinc present in bone and 60 percent in muscle. The highest concentrations occur in eyes, hair, male reproductive organs and bone. Intermediate levels are present in liver, kidney and muscle (Table 1). In blood, 80 percent of the zinc is found in the erythrocytes, mainly as red blood cell carbonic anhydrase. Plasma zinc levels range from 70 to 110 $\mu$g per dl, serum zinc levels are approximately 10 percent higher. The normal range of plasma zinc concentrations varies, consequently it is important to know each particular laboratory's range before deciding if a patient has hypozincemia. Of the plasma zinc, approximately 50 percent is freely exchangeable, being loosely bound to albumin. Another 7 percent is amino-acid bound, mainly to histidine and cysteine. The remaining plasma zinc is tightly bound to alpha 2-macroglobulins, and to other serum proteins. Transferrin can also bind zinc and might play a role in the distribution of zinc in the portal venous system.[7]

## Biochemistry and Physiological Role

More than 20 different zinc metalloenzymes have been identified, the first one being carbonic anhydrase which was found in 1940 to contain 0.3 percent zinc. In mammalian tissues carboxypeptidase A and B, alkaline phosphatase, alcohol

TABLE 1.—*Zinc Concentrations in Human Tissues and Body Fluids**

| *Tissue or Fluids* | *Zinc Concentration (µg/gram wet weight)* |
|---|---|
| Adrenal | 6 |
| Blood | 7 |
| Bone | 66 |
| Brain | 13 |
| Gastrointestinal tract | 21 |
| Hair | 175 |
| Heart | 27 |
| Kidney | 37 |
| Liver | 38 |
| Lymph nodes | 14 |
| Muscle | 48 |
| Ovary | 12 |
| Plasma | 0.7 |
| Prostate | 87 |
| Skin | 6 |
| Spleen | 19 |
| Sperm | 125 |
| Urine | 0.3 |

*Values adopted from References 5 and 6.

dehydrogenase, retinene reductase and lactic-, glutamic- and d-glyceraldhyde-3-phosphate dehydrogenase are known zinc metalloenzymes. Superoxide dismutase contains two atoms of zinc and two atoms of copper. The latter enzyme, also known as erythrocuprein, protects cellular structures from damage by superoxide radicals, generated for example, in the oxidation of xanthine to uric acid by xanthine oxidase.

In addition to both the structural and catalytic functions that the metal exerts in these metalloenzymes, zinc plays an important role in nucleic acid metabolism and protein synthesis. In zinc-deficient animals, the *in vivo* incorporation of thymidine into DNA is decreased and the activities of thymidine kinase, and nuclear DNA-dependent RNA polymerase are reduced. Ribonuclease activity is inhibited by zinc, suggesting that an adequate zinc supply is necessary to prevent excessively rapid RNA degradation. Normal polysome formation is also diminished in the brains of zinc deficient rats.[8] These experimental findings show the essentiality of zinc in the processes of nucleic acid metabolism, protein synthesis and cell division.

Experimental zinc deficiency has been produced in many animal species and also occurs in field conditions. Since the zinc requirements of young growing animals are relatively large, the effects of nutritional deficiency are more striking. Many of the experimentally produced features have now been described in humans. Prominent findings include growth failure and anorexia. Food intake decreases and growth velocity diminishes quickly. The growth inhibition results partly from decreased food intake, but also from impaired utilization since attempts at forced feeding lead to worsening in the condition. The anorexia resolves rapidly after zinc supplementation of a deficient diet.

Hypogonadism with absent spermatogenesis and failure of development of primary and secondary sex organs in males and adverse effects on reproductive processes in females are regularly found in experimentally induced zinc deficiency. Even short-term zinc deficiency in pregnant rats results in a multitude of congenital malformations, particularly of the central nervous system and abnormalities in preimplantation embryos have been elicited by maternal zinc deficiency in the early stages of pregnancy.[9]

In zinc deficient animals epidermal changes are pronounced, with alopecia, dermatitis and disorders of keratinization. Skeletal changes include bowing of legs and stiff joints. Hypoplasia of lymph nodes and thymus has been observed, therefore indicating a requirement of zinc for normal development of immune functions. Impaired mobilization of hepatic vitamin A stores results in decreased serum levels in zinc deficient rats.

## Metabolism

Absorption of zinc occurs mainly in the duodenum and the proximal small intestine. The mechanism probably involves an active transport, facilitated by low molecular weight ligands of pancreatic origin. The ligands bind zinc and transport it to the luminal surfaces of the intestinal epithelial cell. From there, zinc is transferred to a binding site on the basolateral membrane, where it becomes available for attachment to albumin and transferrin proteins in the portal circulation.[10] The percentage of dietary zinc absorbed varies from 20 percent to 80 percent with most reported values approximating 20 percent to 30 percent. Absorption depends partly on the existing nutritional status and partly on the level of intake. Preexisting deficiency enhances absorption, which is also affected by the physical and chemical properties of the diet. Zinc from animal sources is generally better absorbed than that from plant products. This is partly due to the phytate content of plants—phytate binding zinc in the intestinal lumen and rendering it unavailable. Fiber apparently exerts a similar effect. In animals, an increase in the calcium content of the diet, in the presence of phytate, reduces the availability of zinc through formation of an insoluble calcium-zinc-phytate complex. Conversely, chelating agents, whether natural such as casein in milk or artificial (EDTA) can compete with phytate and increase availability.

Other metals may also interfere with absorption, copper and zinc being mutually antagonistic. Both metals possess a common path in absorption, when they attach to a sulfhydryl-rich protein in the cytosol of duodenal mucosal cells. This protein, one of the metallothioneins, has a molecular weight of approximately 10,000 daltons. Cadmium, which also attaches to metallothioneins, similarly interferes with zinc absorption in animals.

Studies with zinc 65 in humans show the presence of the isotope in plasma within 15 minutes of oral administration, peak levels being reached within two to four hours. The highest turnover and retention of radioactive zinc occur in the liver, kidneys and spleen. Most of the hepatic zinc is present in the cytosol, bound to hepatic metallothionein. Muscle and red blood cell uptake of the isotope is slower with bones, brain and hair showing even slower turnover rates. Twenty-one days after administration of the isotope 70 percent had been excreted in the feces, 2 percent in urine and 28 percent remained in the body.

The main route of excretion of zinc occurs in the intestine. Fecal zinc consists mainly of unabsorbed dietary zinc with a small contribution from intestinal cell shedding and zinc of biliary and pancreatic origin. Fecal losses of zinc in adults consuming 15 mg of dietary zinc, approximate 10 mg a day.

Urinary losses of zinc are between 0.3 and 0.5 mg per 24 hours, primarily as amino-acid bound zinc with some porphyrin-bound zinc. Glomerular filtration of amino-acid bound plasma zinc would result in excretion of approximately 2 mg per day, consequently a mechanism for tubular reabsorption of amino-acid bound zinc must exist.[5] The zinc concentration in sweat approaches 115 $\mu$g per dl and under conditions of extreme heat, losses of 2 to 3 mg per day may occur.

## Nutritional Requirements

Zinc is considered to be an essential nutrient, which means that a minimal daily intake must be provided for maintenance of optimal health. There are no reserve stores of zinc, such as ferritin for iron, and the large quantities of zinc found in bone and muscle do not seem to be readily available for mobilization. The Food and Nutrition Board, National Research Council, National Academy of Sciences, added zinc to the list of Recommended Dietary Allowances in 1974.[11] The recommended daily intakes are 3 mg for infants, from birth through 4 months of age and 5 mg from 5 through 12 months. Toddlers and children—1 to 10 years old—should receive 10 mg daily. An intake of 15 mg of zinc is recommended for adolescent and adult males and females, but for the latter requirements increase to 20 and 25 mg, respectively, during pregnancy and lactation.

The availability of zinc in the diet varies with the nature of foods, with zinc from animal sources being generally more available for absorption than that from plant products. Shellfish contain high concentrations of zinc, meats and nuts are good sources and while grains and raw sugars contain adequate quantities of zinc, partitioning of the grains and refining of the sugars will remove most of the available zinc. Large variations in daily intakes, from 5 to 29 mg per day, have been reported for men.[12] Representative zinc concentrations of a variety of foods are shown in Table 2.

## Zinc Deficiency in Humans

In the last 20 years there have appeared increasing numbers of reports of beneficial effects of zinc supplementation in a variety of disease states. These studies have shown the importance not only of an adequate nutritional intake of zinc, but also of the bioavailability of dietary zinc. The major effects of zinc deficiency in humans are changes in growth, sexual maturation and function, appetite, the senses of taste and smell, epithelial structures and processes such as wound healing. There is also growing interest in the roles that metals such as iron and zinc play in the processes of cognitive and psychological function and in the maintenance of normal immunocompetence. Historically, human zinc deficiency was first reported from Middle Eastern countries, and this discovery created impetus for further research.

### *Adolescent Dwarfism in Middle Eastern Countries*

Prasad and collaborators in 1961 described a new syndrome of dwarfism with anemia, hepatosplenomegaly and hypogonadism, and they postulated that zinc deficiency was the causative factor of the lack of growth and sexual maturation.[4] This report originated from Iran where nutritional dwarfism is found among approximately 3 percent of male inhabitants of rural villages. These adolescents and young men generally have the physical appearance of 10-year-old boys, with growth retardation and absent sexual development. They often have a rough skin and spoon nails, the bone age is delayed and the epiphyses of long bones remain open. Anemia and hepatosplenomegaly were concomitant findings and both were corrected with administration of iron. Most of the subjects in Iran were clay-eaters, some complained of lack of appetite and two of the original ten patients had night blindness. A serum zinc level was obtained in only one patient and was found to be low. A similar syndrome was found in Egypt, where, however, the anemia was not so profound and the hepatosplenomegaly less pronounced. Studies of zinc metabolism in Egyptian dwarfs showed decreased zinc levels in plasma, red blood cells and hair, a diminished exchangeable zinc pool, and decreased excretion of radioactive zinc in urine and feces, the latter finding being indicative of zinc conservation in a deficiency state.[15] The pathogenesis of the iron and zinc deficiency was investigated and three possible causes were envisaged. The diet of the Iranian and Egyptian dwarfs consisted mainly of unleavened wheat bread, which has a high phytate content. The latter can bind dietary iron and zinc and render them unavailable for intestinal absorption. In some patients, increased urinary blood losses from schistosomiasis with subsequent excretion of iron and zinc was considered to be another cause. Third, in hot climates excessive sweating could also enhance zinc losses and lead to a deficiency state. There followed considerable controversy on the role that zinc-deficiency had in this syndrome, until, in 1972, Halsted and collaborators published the results of a controlled study of zinc supplementation in 14 such dwarfs.[16] The subjects who received zinc supplements, in addition to a well-balanced diet, showed greater growth velocities and earlier onset of sexual maturation than the controls who received the well-balanced diet alone. The unleavened breads eaten by the Iranian villagers, whose diet contained little animal protein, were further found to contain 40 percent more phytate than the leavened breads consumed by urban inhabitants, presumably because fermentation destroys phytate.

TABLE 2.—*Examples of Zinc Content of Individual Food Items**

| *Foods* | *Zinc Content: mg/100 grams* |
|---|---|
| Beef: round steak | 5.0-6.00 |
| Liver | 3.80 |
| Chicken | |
| leg | 2.80 |
| breast | 0.90 |
| Oysters | |
| Atlantic | 74.70 |
| Pacific | 9.00 |
| Whitefish | 1.00 |
| Tuna: canned | 1.00 |
| Peanuts and peanut butter | 2.90 |
| Wheat: whole grain | 3.40 |
| Bread | |
| whole wheat | 1.80 |
| white | 0.60 |
| Rice: polished | 0.4-0.70 |
| Lima beans | |
| raw | 2.80 |
| cooked | 1.00 |
| Peas | 0.70 |
| Potato chips | 0.81 |
| Carrots | 0.40 |
| Butter | 0.10 |
| Milk | 0.35 |
| Corn oil margarine | 0.20 |
| Cheese: domestic mozarella | 3.88 |
| Orange juice | 0.07 |

*Data from References 12, 13 and 14.

### *Wound Healing*

If one considers that wound healing is a process in which active cell growth and protein synthesis are occurring, it is not surprising that a deficiency of a nutrient essential for normal growth would result in impaired wound healing.[17] Animal studies showed that zinc supplementation accelerated the rate of healing of surgical wounds, mainly through enhancement of the rate of epitheliazation. Conversely, zinc-deficient animals show striking changes in epidermal and epithelial structures. In humans, zinc supplementation has allowed healing of chronic leg ulcers and indolent wounds which were previously refractory to treatment.[17] While some contradictory results were obtained in studies on the effects of zinc in healing, there is now general agreement, that zinc supplementation will improve the rate of healing in patients with laboratory evidence of inadequate zinc nutriture. Clinical experience shows that patients with malnutrition, malignant conditions, pulmonary infections and atherosclerosis heal poorly. Massive urinary losses of zinc occur after major burns, and zinc deficiency occurs frequently in patients in hospital as a result of poor nutritional intake previously and of derangements in zinc homeostatic metabolic functions with increased urinary and fecal losses. In the presence of delayed healing, laboratory evaluation of zinc status should be accomplished and supplementation considered. This subject is covered in an excellent review by Pories and co-workers[18] who recommend 220 mg of zinc sulfate heptahydrate (45 mg $Zn^{++}$) three times per day. These quantities of zinc correct hypozincemia and enhance wound closure in zinc-deficient subjects. Pories has also reported that zinc supplementation decreased the time required for healing of pilonidal cyst surgical wounds in young adults. Also of interest is a report from Australia where zinc supplementation improved the frequency and rates of healing of gastric ulcers.[19]

*Zinc and the Senses of Taste and Smell*

Many diseases are accompanied by decreased taste (hypogeusia) and smell acuities (hyposmia) and distortions of taste (dysgeusia) and smell (dysosmia) can also occur. While these complaints are often of short duration—during upper respiratory infections, acute hepatitis or the first trimester of pregnancy—they sometimes persist, and may be most inconvenient and lead to weight loss.[20] Hypogeusia can occur during copper depletion with D-penicillamine and can be corrected by the administration of exogenous copper or zinc. These observations led to the empirical administration of zinc sulfate to patients with disorders of taste and smell and the results of the initial placebo-controlled study seemed encouraging. However, in a later double-blind study both zinc sulfate and placebo were found to exert equivalent effects.[21] Anorexia and hypogeusia appear rapidly, though, when zinc depletion is experimentally produced, through administration of 1-histidine for example, a microligand that enhances urinary zinc losses.

The importance of zinc in the maintenance of taste acuity and of a normal appetite was also shown in children by Hambidge and associates.[22] These authors carried out a survey of trace element concentrations in hair and they found that ten of a group of 132 apparently normal children, aged 4 to 16 years, had hair zinc levels less than 70 $\mu$g per gram, more than 3 SD below the adult mean and in the range of hair zinc levels of Middle Eastern dwarfs. When additional information was obtained, eight of the ten children were noted to be below the 10th percentile for height, with the poor growth not explainable on a familial basis. These children were described as poor eaters, with a particular distaste for meats, and objective hypogeusia was shown in five of the six children in whom taste acuity was measured. Supplementation with small doses of zinc (0.2 to 0.4 mg per kg of body weight per day) was followed by correction of the taste acuity defects within one to three months. The authors concluded that these apparently normal children were suffering from a dietary deficiency of zinc, sufficient to impair taste acuity and possibly also sufficient to decrease appetite and limit growth velocity.

*Zinc and Growth of Infants and Children*

In the same survey of hair zinc concentrations, Hambidge and co-workers found that infants and young children had hair zinc levels much lower than at birth, where hair zinc levels equaled adult levels. The plasma zinc levels of infants in Denver were also found to be lower than mean adult levels, a finding which differed with reports from other countries.[23] These observations prompted a search for explanations, one of which was the relatively low zinc content of some American infant milk formulas. In the fabrication of these formulas skimmed cow's milk is diluted to reduce the protein content to levels closer to those of human breast milk. This dilution is accompanied by a concomitant reduction in zinc content, to a final concentration of 1.8 mg per liter, whereas most whole milks contain 3 to 4 mg per liter.

There followed a study on the effects of supplementing Similac with 4 mg of elemental zinc per liter. This study was done in a double-blind controlled manner with anthropometric measurements and determinations of plasma zinc levels at determined intervals.[24] One surprising observation was that male infants receiving the zinc-supplemented product had significantly larger increments in length and weight gains than the control infants, receiving the nonsupplemented formulas. The test and control female infants did not show any differences in growth rates. The results suggested that zinc requirements of growing male infants may be higher than for females, a finding previously noted in two animal species, and that the zinc content of the formulas, before 1975, when supplementation was started, was insufficient to ensure optimal growth of male infants.

Marginal zinc deficiency in children had been found in Iran, where a controlled trial of zinc supplementation resulted in significant differences in height and weight gains and in bone age maturation, together with a tendency towards accelerated maturation of sexual development.[25] Marginal zinc deficiency, however, was not suspected in this country until recently, when Sandstead[3] calculated that infants, pregnant women, teenage and college women, and elderly persons in institutions were living on diets of marginal or deficient zinc content. Support for this hypothesis is coming from nutritional studies of varied American population groups including vegetarians,[26] elderly persons,[27] and preschool children from low-income families.[28] Decreased mean levels of zinc in plasma and hair were found in a group of Denver preschool children who were selected, upon entry to Head Start schools, because of low growth percentiles. Whether zinc-supplementation will improve growth velocities in such children subsisting on low-income budgets remains yet to be determined.

### *Acrodermatitis Enteropathica*

Acrodermatitis enteropathica is a rare disease, of autosomal recessive inheritance, the onset of which occurs during infancy. Gastrointestinal dysfunction with diarrhea and vomiting, extensive acral and periorificial skin lesions of eczematous or vesicular-bullous type, and alopecia are the principal clinical findings. Growth retardation, paronychia with nail dystrophy, ocular symptoms of blepharitis, conjunctivitis and corneal opacities, stomatitis, cheilitis and emotional lability also occur frequently. The time of onset depends on the presence and duration of breast-feeding, clinical manifestations generally appearing one or two weeks after weaning. If susceptible infants are not breast-fed the symptoms will develop in the first four to ten weeks of life. Secondary intercurrent infections with bacteria and yeast, combined with progressive malnutrition often resulted in death within one to three years of life. In 1953 the usefulness of 8-hydroxyquinoline derivatives was shown for the control of symptoms; the mechanisms were unknown but now are thought to be related to the chelating properties of these compounds, which enhance intestinal zinc absorption.[29] In 1973 Moynahan recognized the similarity between the findings in acrodermatitis enteropathica with those of experimentally induced zinc deficiency in animals.[1] This observation occurred during the course of treatment of a child with lactase deficiency in addition to acrodermatitis enteropathica, who was maintained on a synthetic diet and on hydroxyquinoline treatment. Relapse of symptoms led to an analysis of the diet which was found to contain very little zinc. Administration of the metal was accompanied by disappearance of lesions, which recurred when the zinc supplement was inadvertently withheld by the patient's mother. Subsequent studies (for a recent review see reference 29) confirmed the presence of a severe zinc deficiency state in this disease, presumably caused by a defect in intestinal absorption of the metal. The defect can fortunately be overcome by the daily administration of 1 to 2 mg of zinc per kg of body weight. This results in bringing to normal levels the laboratory indicators of zinc nutrition and is accompanied by catch-up growth spurts in prepubertal children.[30] Prolonged administration of human milk was another therapeutic modality which was used in patients with this disease who could not tolerate hydroxyquinoline derivatives. Studies by Dr. Hurley's group[31] have shown that zinc in breast milk is bound to a low molecular weight protein which seems to enhance intestinal zinc absorption, therefore providing an explanation for the therapeutic effect of breast milk. There has been a recent report on a variant of acrodermatitis enteropathica without hypozincemia in which abnormally high concentrations of zinc were found in serum, epidermis and dermis.[32] This variant may represent another disorder of zinc metabolism, where intracellular zinc is chemically bound and unavailable for biologic activity.

### *Hereditary Hyperzincemia*

Another inherited disorder of zinc metabolism was described in 1976 when Smith and collaborators[33] studied the family of a 28-year-old black man in whom levels of zinc in plasma were found to be extremely high (greater than 300 $\mu$g per dl). Elevated plasma zinc levels were found in four of the patient's siblings, in his son and in one of his two nieces. Fractionation of serum proteins showed that most of the excess zinc was bound to albumin, and the results of a test zinc load showed that the binding capacity of the serum proteins was not saturated. The zinc levels of hair, nails and erythrocytes were normal in this subject. While hyperzincemia is a rare finding, it should no longer be dismissed as simple contamination of a blood sample.

*Acute Zinc Deficiency With Total Parenteral Nutrition*

Kay and Tasman-Jones in 1975 described a syndrome which resembled acrodermatitis enteropathica and occurred during intravenous hyperalimentation with solutions containing only trace amounts of zinc.[34] The clinical findings were periorificial dermatitis, diarrhea, alopecia and pronounced depression. Massive hyperzincuria, up to 25 mg per day was noted in one of the patients following a period of prolonged catabolism complicated by sepsis. The hyperzincuria decreased when the patients were gaining weight, but at that time the plasma zinc levels fell and the clinical symptoms appeared. Later studies have shown increased urinary zinc excretion during parenteral nutrition, presumably caused by an excess amount of amino acid bound zinc being presented for tubular reabsorption.[35] In patients receiving parenteral alimentation, the development of periorificial rashes, depression, alopecia or diarrhea indicates the necessity of laboratory evaluation of zinc metabolism. The response to zinc supplements is rapid with mood improving first and skin changes thereafter.

*Zinc and Immunocompetence*

Impaired cellular immunity has been noted in zinc deficient animals and similar findings are being reported in humans. Pekarek and co-workers showed there to be impaired delayed skin reactivity to dinitrochlorobenzene and depressed lymphocyte transformation capacity in a 17-year-old boy with acquired zinc deficiency.[36] A normal lymphocyte response and delayed skin reaction were obtained three weeks after zinc therapy. Supplementation in eight children who had recovered from protein-energy malnutrition with 2 mg of zinc per kg of body weight per day was accompanied by significant increases in thymic size, as judged by chest radiological examinations.[37] In an extension of their previous studies, Golden and associates measured delayed-hypersensitivity reactions in ten children with protein-energy malnutrition using skin tests with Candida antigen.[38] Each child served as his own control, one arm being covered with a placebo ointment, the other with 1 percent zinc sulfate in the same emulsifying ointment. It is known that zinc can be absorbed transcutaneously from zinc sulfate ointments and the delayed hypersensitivity responses were larger at the zinc treated injection sites. The degree of enhancement of the response correlated negatively with the plasma zinc concentration at the time of testing. These studies indicate that zinc deficiency depresses T-cell response and, therefore, may be a factor in the increased susceptibility to infections in conditions such as protein-energy malnutrition. Impaired monocyte and neutrophil chemotaxis has also been shown in acrodermatitis enteropathica, with correction of the defects with zinc treatment.[38]

*Sexual Function in Renal Failure*

Antoniou and her colleagues carried out an elegant controlled study on eight impotent men being treated for renal failure by hemodialysis.[40] Four of the impotent subjects received zinc supplements orally for six months, but there was only a slight increase in the previously low plasma zinc levels. Zinc chloride was then added to the dialysis solution in amounts sufficient to maintain the plasma zinc levels between 100 and 150 mg per dl. Within two to four weeks there was a striking improvement in potency in the four patients, which was accompanied by an increase in testosterone and follicle stimulating hormone values in plasma to normal levels. No changes were noted in the four patients receiving placebos. This observation confirms the importance of zinc for normal function of the pituitary-testicular hormonal axis and suggests that zinc deficiency may be a reversible cause of sexual dysfunction in subjects with renal failure. The causes of zinc deficiency in such subjects still remain unclear.

In another study of male subjects with oligospermia, zinc supplementation was accompanied by increased levels of plasma testosterone and increase in sperm count.[41] These impressive findings should provide impetus for further research on zinc metabolism in patients with reproductive dysfunctions.

*Zinc and Chronic Liver Disease*

Zinc and chronic liver disease is a complex subject which has been recently reviewed by Sullivan and Burch.[42] For more than 20 years it has been known that patients with cirrhosis had decreased levels of zinc in plasma and increased urinary excretion of zinc. The reasons for the latter are not well understood but may relate to changes in the quantities of amino acid bound zinc circulating in the plasma compartment. In

TABLE 3.—*Etiological Factors in Zinc Deficiency*

| *Factors* | *Examples* |
|---|---|
| Inadequate dietary intake ... | Low-income diets<br>Old age<br>Protein-calorie malnutrition |
| Increased zinc requirements . | Rapid growth<br>Pregnancy<br>Lactation<br>Tissue anabolism |
| Decreased availability ...... | Phytate<br>Fiber |
| Decreased absorption ....... | Malabsorption syndromes<br>Steatorrhea |
| Excessive losses ........... | Hyperzincuria<br>Surgery<br>Burns<br>Increased sweating<br>Blood losses |
| Iatrogenic ................ | Chelating drugs (penicillamine)<br>Parenteral nutrition |
| Genetic defects ............ | Acrodermatitis enteropathica |

alcoholic persons the dietary zinc intake would be expected to be marginal, which, with increased excretion, would facilitate the development of a zinc deficiency state. Zinc is a component of alcohol dehydrogenase which, in the liver, catalyzes the first step of alcohol metabolism, and in the retina regenerates retinal aldehyde from retinol. The latter mechanism is necessary for adaptation to darkness. Abnormalities of dark adaptation are frequently found in alcoholics with cirrhosis and respond to both supplementation with zinc[43] and with vitamin A.[44] Interactions between zinc and vitamin A metabolism have been shown in rats, in which the mobilization of hepatic stores of vitamin A is a zinc-dependent process.[45] By facilitating the synthesis of retinol-binding protein, one of the vitamin A plasma transport carriers, zinc may be exerting its beneficial effect in reversing night blindness, although a direct effect on retinal alcohol dehydrogenase is not to be excluded.

Another relation between zinc and liver disease that deserves further study derives from the observation that ornithine transcarbamylase activity is decreased in zinc deficient animals. Elevations of blood ammonia and decreased levels of blood urea nitrogen are also found in cirrhotic patients. Consequently, in the treatment of alcoholic patients zinc supplementation should certainly be considered in addition to correction of other nutritional deficiencies.

### *Other Conditions Associated With Zinc Deficiency*

Zinc deficiency states can develop in many circumstances and some of the etiological contributory factors are summarized in Table 3. Retarded growth with delayed puberty can occur in sickle-cell disease patients, where excessive urinary zinc losses result from increased red blood cell destruction.[46] Similarly, the adolescent dwarfism syndrome has been described in patients with intestinal malabsorption[3] and most recently with cystic fibrosis.[47] In rheumatoid patients encouraging results were found with zinc sulfate supplementation. Low serum zinc levels had previously been noted in rheumatoid arthritis by other investigators and the study with zinc supplementation was based on the premise that zinc is necessary for normal synovial function and also to facilitate host-resistance to the disease process.[48]

### *Skin Diseases and Zinc*

Michaelson[49] started using zinc supplements in patients with acne after noting that in one of his patients with acrodermatitis enteropathica there was a pronounced decrease in acne lesions after onset of treatment with zinc. Two controlled studies have thereafter shown that orally given zinc sulphate was a useful therapeutic agent in the treatment of acne. In one of the studies both zinc and tetracycline caused a 70 percent decrease in acne scores.[49,50] Scribner has also recommended zinc supplements in low doses for persons with socially unacceptable perspiration odor.[51]

## Diagnosis of Zinc Deficiency States

The diagnosis of zinc deficiency is not an easy one. Zinc levels in plasma are decreased in many acute situations. In an elegant study, Falchuk showed that the decrease in zinc levels in plasma was caused mainly by a decrease in albumin-bound zinc, an effect that could be reproduced by adrenocorticotropic hormone (ACTH) infusions.[52] Whether the decreases in plasma zinc caused by leukocyte proteins and endotoxins[53] is mediated through ACTH remains yet to be determined. Persistence of decreased levels of zinc in plasma after an acute illness probably represents a good indicator of a deficiency state. Determination of hair and erythrocyte levels of zinc may be useful in conditions in which zinc deficiency has been of long duration. The measurement of urinary zinc excretion may be helpful. If the urinary zinc values are high in the presence of decreased plasma levels, this would indicate disturbances of zinc metabolism. If the urinary levels of zinc are low, it may be indicative of body conservation.

In the presence of poor growth, decreased appetite, lack of smell, poor wound healing, impaired sexual maturation or function, zinc deficiency should be considered. Diminished night vision in alcoholics and depressed mood in elderly persons may be indicators of marginal deficiency. Perhaps measurement of delayed skin sensitivity with topical application of zinc sulphate ointment may be useful to detect borderline deficiency states. The response to zinc supplements will often provide an answer as to whether the patient was in some degree zinc deficient.

## Treatment of Zinc Deficiency States

Zinc is well absorbed as the oxide, carbonate, sulfate or metal. The sulfate is generally used at doses of 5 to 10 mg per kg of body weight per day, which provide 1 to 2 mg of zinc per kg of body weight per day. Lesser doses may sometimes be used. In surgical patients receiving 220 mg of zinc sulfate three times a day, 5 percent reported gastrointestinal upsets that ceased when treatment was stopped. No side effects have been reported with doses of 1 mg of zinc per kg of body weight per day. Administration of zinc supplements with meals decreases the incidence of gastrointestinal symptoms, but may adversely affect zinc absorption.

Intravenous requirements for patients receiving parenteral alimentation remain yet to be determined exactly. They approximate 30 to 40 $\mu$g per kg of body weight per day. Intravenous dosage for correction of deficiency states has not really been determined, either, and many patients can tolerate oral administration of zinc supplementation even in short bowel syndromes.

## Toxicity

Zinc is relatively nontoxic and a good margin exists between physiologic requirements and toxic doses. Zinc toxicity with diarrhea and vomiting has occurred in persons drinking lemonade mixed in galvanized cans. Zinc fever has been described accompanied by profound anemia in a patient receiving hemodialysis with zinc contaminated water. Acute intravenous zinc poisoning resulting in death occurred after the inadvertent administration of 7.4 grams of zinc sulfate intravenously.[54] However, ingestion of 12 grams of metallic zinc by a 16-year-old boy resulted only in pronounced lethargy.[55]

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## Glomerular Filtration Rate as a Useful Measurement in Patients With Sepsis

I THINK one of the most useful measurements you can make in a patient with sepsis or any other patient is the glomerular filtration rate (GFR)—just a one-hour creatine and clearance determination. Any laboratory will do it; it is simple to do. Once you have gotten the GFR up to normal, because of the phenomenon of autoregulation you cannot drive it any higher no matter how much fluid you give. And it is the GFR that determines how much nitrogen is going to be excreted. So I think the answer is that when you have given enough fluid, so that the GFR is up to a relatively normal value for that patient, further fluid cannot possibly be of any value in clearing nitrogenous wastes.

—SAMUEL R. POWERS, JR., MD, *Albany, New York*
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